REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. EXAMINER INTERVIEW, CLAIM STATUS & AMENDMENTS

Applicants sincerely thank Examiner Hong for holding a telephone interview on May 13, 2008. The claims have been amended along the lines discussed during the interview.

Claims 1, 2, 4-13, 16, 17 and 20-27 were pending in this application when last examined.

Claims 1, 2, 4-13 and 27 were examined on the merits and stand rejected.

Claims 16, 17 and 20-26 were withdrawn as non-elected subject matter.

Claims 1 and 27 are amended to recite that the purified antigen is selected from the group consisting of purified proteinaceous substances, purified non-proteinaceous substances, purified proteinaceous substances linked to a carrier, purified non-proteinaceous substances linked to a carrier, and fragments thereof. Applicants note support for this amendment, and the definitions of these terms, can be found on page 3, line 30 to page 4, line 12, of the specification as filed.

Claims 28-31 are newly added. Support for such claims can be found on page 3, line 30 to page 4, line 12, of the specification as filed.

No new matter has been added.

Applicants further note that the above-noted amendment was not submitted to the Office earlier as the previous Office Action's rejections did not clearly set forth the technical reasons for the current obviousness rejection. In particular, on page 7 of the Office Action of July 24, 2007, it is stated:

> Thus, since Mather et al. teach the immunization of an animal with a plurality of viable and intact cells that constitute cell surface antigens anchored to the plasma membrane, which upon immunization induce an immune response and result in antibody production; the plurality of cells expressing different cell surface antigens reads on the instantly claimed "plurality of candidate antigens." (Emphasis ours)

Thus, a fair reading of this passage indicates that each cell is composed of a plurality of antigens. Hence, the amendment "purified antigen" should have overcome this rejection as whole cells are not purified antigens. Thus, the Applicants were surprised during the interview with Examiner Hong, that the current rejection was not overcome by previous amendments to the claims since "antigen" was interpreted as including whole cells. Thus, Applicants respectfully request the Examiner to enter the above claim amendments since Applicants feel they did not have a fair chance to fully respond to the rejection of record as such rejection lacked clarity.

II. OBVIOUSNESS REJECTION

In item 9 on pages 3-9 of the Office Action, claims 1, 2, 4-13, and 27 remain rejected under 35 U.S.C. § 103(a) as obvious over Mather et al. (WO 2000/037503) in view of Kucherlapati et al. (US 6,150,584), van de Winkel et al. (US2003/0138421, published July 24, 2003), Rava et al. (US 6,720,149), and Kessler et al. (US 2003/0044849).

Applicants respectfully traverse this rejection as applied to the amended claims.

Applicants note that the term "purified candidate antigen" has now been further defined as "purified proteinaceous substances, purified non-proteinaceous substances, purified proteinaceous substances linked to a carrier, purified non-proteinaceous substances linked to a carrier, and fragments thereof", in order to expedite allowance.

Thus, the claimed invention is directed towards producing multiple monoclonal antibodies against multiple known purified antigens simultaneously by immunizing with multiple purified antigens wherein the antigens are selected from the group consisting of purified proteinaceous substances, purified non-proteinaceous substances, purified proteinaceous substances linked to a carrier, purified non-proteinaceous substances linked to a carrier, and fragments thereof, generating hybridomas and screening the supernatants of the hybridomas on protein chips displaying the antigens.

In the Office Action, Mather was used as the primary reference in the obviousness rejection and it was combined with Kucherlapati, van de Winkel, Rava and Kessler.

Mather relates to a method of generating a group of monoclonal antibodies that are representative of a specific cell type and that will not cross-react with other cells (see abstract). Mather discloses immunizing an animal with **intact** cells and producing hybridomas from the animal (see p17, lines 27-34). See also the paragraph 2 of the Summary of the Invention of Mather. The supernatant of the hybridomas is screened by ELISA against the **intact** cells with which the animal has been immunized to identify a population of monoclonal antibodies characteristic of the cells that have been used to immunize the animal (p18, lines 12-20). The specific target antigens on the cell to which the monoclonal antibodies in this population bind may then be identified, if desired, by immobilizing the antibodies on a column, adding purified antigens and eluting antigens that are bound to the antibodies (p21, l6-10).

Accordingly, Mather does not describe immunization of mammals with purified antigens selected from purified proteinaceous substances, purified non-proteinaceous substances, purified proteinaceous substances linked to a carrier, purified non-proteinaceous substances linked to a carrier, and fragments thereof. In particular, Applicants note that "purified" in the specification is defined as "substantially free from any other components" (see page 3 of the specification). Thus, purified proteinaceous substances, purified non-proteinaceous substances, purified proteinaceous substances linked to a carrier, purified non-proteinaceous substances linked to a carrier, and fragments thereof does not include within its scope whole cells which have substantially other components.

Further, it is clear from paragraph 3 of the Background of the Invention of the reference, that Mather considers extraction of purified antigens for use as immunogens to be **disadvantageous**. In this sense, Mather **teaches away** from the present invention and there would be no motivation to modify the teachings of the combined cited references to arrive at the claimed invention.

Again, Mather differs from the claimed invention in both the immunization method (i.e., **whole cell vs purified proteinaceous substances, purified non-proteinaceous substances, purified proteinaceous substances linked to a carrier, purified non-proteinaceous substances linked to a carrier, and fragments thereof**) and in the screening method to isolate monoclonal antibodies (i.e., **ELISA using whole cells vs protein chips displaying purified antigens**).

Further, in Mather, the identity of the antigens on the **whole cells** against which the monoclonal antibodies were being generated was **not** known. Applicants note that in the last response the Examiner contended that the antigens are known because the cell types are known. Applicants strongly disagree as Mather fails to disclose which antigens are on the cell surface. The point of Mather is to generate a population of monoclonal antibodies against **unknown** antigens on the **whole cells** with which the animal is being injected. The identity of the antigens on the cell surface to which the population of monoclonal antibodies that are generated by immunization bind is optionally established at a later stage by screening immobilized antibodies against candidate antigens.

Accordingly, it is clear that Mather fails to disclose or suggest immunization of animals with a plurality of **purified** antigens as defined in the claims, generating immortalized cell lines, and then screening the supernatant of the cell lines against protein chips on which the **purified** candidate antigens are displayed.

Moreover, there would be no motivation for the skilled person to replace immunization with **whole cells** in Mather with immunization with **purified** candidate antigens as defined in the claims, because the skilled person in Mather did not know the identity of the antigens to which monoclonal antibodies were being generated, and would not therefore know what purified antigens to use for immunization in place of the whole cells. The skilled person would not simply select random purified antigens that he thought might be expressed on the surface of the whole cells for immunization since this would not achieve the primary aim in Mather of

generating a population of monoclonal antibodies representative of a specific whole cell which does not cross-react with other whole cells. For this same reason, one of ordinary skill in the art would **not** have replaced screening monoclonal antibodies against **whole** cells with screening against **purified** antigens selected from purified proteinaceous substances, purified non-proteinaceous substances, purified proteinaceous substances linked to a carrier, purified non-proteinaceous substances linked to a carrier, and fragments thereof.

The remaining cited references fail to make up for the deficiencies in Mather for the following reasons.

Kucherlapati fails to disclose or suggest immunization of animals with a plurality of purified antigens to simultaneously produce monoclonal antibodies against a plurality of purified antigens. Further, Kucherlapati does not disclose or suggest the identification of monoclonal antibodies against multiple antigens using a protein chip displaying the purified antigens.

Instead, Kucherlapati discloses immunization of a transgenic mouse having a human immune system (Xenomouse) with a **single** purified antigen, not a **plurality** of **purified** candidate antigens. A **single** antigen is used to immunize the transgenic mouse (column 4, lines 41-50), and B cells from the immunized mouse are used to generate hybridomas producing monoclonal antibodies against this single antigen using Kohler & Milstein's standard method (column 7). Monoclonal antibodies binding to the antigen are identified by screening using a sandwich ELISA (column 7).

All of the examples in Kucherlapati describe immunization of the animal with a **single** antigen followed by generation of hybridomas and identification of monoclonal antibodies binding to the antigen using standard ELISAs. In particular, Example 9 (referred to by the Examiner) discloses immunization of the mouse with recombinant IL-8 (column 18, lines 15-20), isolation of spleen cells and generation of hybridomas (column 18, lines 35-50) and identification by ELISA of hybridomas producing monoclonal antibodies that bound IL-8 (column 18, lines 55-62).

Example 9 previously referred to by the Examiner discloses immunization of the Xenomouse with IL-8 (i.e., a single antigen) and generation of hybridomas from spleen cells. The supernatant of these hybridomas is screened against IL-8 by ELISA (not protein chips) to identify monoclonal antibodies binding IL-8 (col 18, l55-60). This is the step of identifying the monoclonal antibody. Only once the monoclonal antibody binding to IL-8 has been identified by ELISA are further experiments conducted to ascertain the properties of the monoclonal antibody that has been isolated. In one of these experiments, recombinant IL-8 is bound to a gold chip and used to investigate the kinetics of the monoclonal antibody using a BIAcore instrument (col 19, l21-27).

Applicants respectfully submit that the Office was incorrect to suggest that the experiment conducted with the BIAcore instrument corresponds to the claimed step of screening the supernatant of hybridomas against protein chips displaying purified antigens used for immunization in order to identify antibodies that bind to the protein chip. Instead, in Kucherlapati, the step of screening the supernatant to identify the antibodies that bind antigen was carried out by ELISA.

Therefore, Kucherlapati differs from the claimed methods in two ways: i) it immunizes with a **single** purified antigen and not with multiple purified antigens; and ii) it discloses identifying monoclonal antibodies that bind to the antigen by ELISA with the antigen and **not by screening using a protein chip** displaying the purified antigen.

Kucherlapati focused on the production of a monoclonal antibody to a **single** antigen. As such, there is no motivation in Kucherlapati to replace immunization with one purified antigen with immunization with multiple purified antigens. Nor is there any suggestion to replace ELISA screening with screening against a protein chip to identify multiple monoclonal antibodies simultaneously.

In fact, the data filed by Applicant show that these changes enable high-throughput production of multiple monoclonal antibodies against multiple antigens simultaneously, a

possibility that had not been contemplated previously. The present invention also has the advantage that it is possible to map where on an antigen any antibody binds by screening every supernatant against multiple antigens, something that is totally impracticable with immunization with a single antigen and screening by ELISA. In this regard, the present invention exhibits unexpected results over the cited prior art reference. Again, none of the cited references provide motivation for these changes nor do they recognize the improvements associated these changes. Accordingly, Applicants were first to realize that these changes would remove the bottleneck in monoclonal antibody production and allow fast and efficient production of monoclonal antibodies against multiple different antigens.

Accordingly, it is clear that Kucherlapati does **not** describe immunization of animals with a **plurality** of **purified** antigens in order to produce monoclonal antibodies against a plurality of purified antigens simultaneously. Also, Kucherlapati does not describe the identification of monoclonal antibodies against multiple antigens using a protein chip displaying the purified antigen.

For these reasons, the invention of the amended claims is novel and non-obvious over the combination of Mather and Kucherlapati.

Van de Winkel fails to remedy the deficiencies of Mather and Kucherlapati.

The disclosure of van de Winkel is similar to Kucherlapati in that it also discloses immunization with a **single** purified antigen (IL-8) to produce monoclonal antibodies that bind to IL-8 and identification of these antibodies by ELISA using IL-8. Accordingly, the comments relating to Kucherlapati are also applicable to van de Winkel.

Rava describes a biological chip plate for conducting multiple biological assays. The plate contains a plurality of wells, each well containing a chip having a molecular probe array. The focus of Rava is on the production of plates containing DNA arrays for use in detecting DNA or RNA molecules. The Applicant does not dispute that protein chips were available

before the filing date, nor that these chips could be used to detect a monoclonal antibody to a particular antigen.

However, there is no discussion at all in Rava of the production of monoclonal antibodies. There is also no suggestion in Rava that a plurality of purified antigens could be displayed on chips simultaneously to detect monoclonal antibodies that bind to a plurality of different antigens. Thus, it is clear that Rava fails to remedy the above-noted deficiencies of Mather and Kucherlapati.

Again, prior to the current invention, no one had realized that vast improvements in terms of speed and efficiency in monoclonal antibody production could be achieved by immunizing with **multiple purified** antigens and then screening with protein chips displaying the **purified** antigens. Where it was desired to produce monoclonal antibodies against known antigens, the standard practice was to follow established methods of immunizing with a single antigen and then screening using an ELISA – this is the situation disclosed in van de Winkel and Kucherlapati.

Therefore, there is no motivation in van de Winkel or Kucherlapati to alter this standard practice and screen supernatant using the protein chips disclosed in Rava, nor to immunize with multiple antigens. Mather does not provide motivation for immunization with multiple antigens, since it relates to immunization with unknown antigens using whole cells, not to the production of monoclonal antibodies against known purified antigens.

Kessler relates to isotyping of monoclonal antibodies. This paper appears to have been cited by the Office as relevant to dependent claims relating to isotyping. As discussed in the last response, Kessler is concerned with methods of producing antibodies by immunization with whole cells or heterogeneous mixtures. There is no teaching or suggestion in Kessler that an animal or animals can be immunized with a plurality of purified antigens to produce monoclonal antibodies against a plurality of purified antigens. Nor is there any suggestion the resulting monoclonal antibodies be screened using protein chips displaying multiple purified antigens.

For these reasons, the cited combination fails to disclose or suggest each and every element of the claimed invention.

Applicants further note that the claimed invention results in enormous advantages over conventional methods of producing a single monoclonal antibody by immunizing an animal with a single antigen, producing hybridoma cells using Kohler and Milstein's method in identifying monoclonal antibodies against the antigen using an ELISA. As evidence of these advantages, Applicants again point to the De Masi et al. paper "published by the inventors" attached to the response of April 30, 2007. This paper presents evidence of unexpected results of the present invention.

The claimed methods enable the production and screening of monoclonal antibodies against large numbers of purified antigens simultaneously. This advantage alone represents huge progress over methods of generating and screening monoclonal antibodies against a single antigen, as disclosed for example, in Kucherlapati. The present invention also enables huge numbers of hybridoma cell supernatants to be screened compared to prior art methods, making it more efficient at identifying high affinity antibodies. The claimed methods are simple and many times faster than conventional methods of the type disclosed in the cited references. The methods claimed are also more economical due to the fact that they require hardly any antigen for use in the screening procedure.

There is no suggestion in any of the other documents cited by the Examiner that an improved method for producing and screening monoclonal antibodies which enables the simultaneous and efficient production of monoclonal antibodies against a plurality of purified candidate antigens could be obtained by immunizing an animal or animals with more than one purified antigen and by screening the monoclonal antibodies produced using protein chips. It might well have been obvious to the skilled person at the priority date that it was desirable to achieve the advantages provided by the methods of the invention but it would not have been obvious how to achieve them.

It is respectfully submitted that such advantageous and unexpected results are indicative of the nonobviousness of the present invention.

Thus, for the above-noted reasons, Applicants suggest that this rejection, as applied to the amended claims, is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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